Drug Monograph

Drug/Drug Class: **Oxtellar XR™ (oxcarbazepine) Tablets / antiepileptic**

Prepared for: MO HealthNet
Prepared by: Xerox Heritage, LLC

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Oxtellar XR™ is available in 150mg, 300mg and 600mg extended-release tablets containing 150mg, 300mg and 600mg respectively of oxcarbazepine. Patheon, Inc., Whitby, Ontario L1N 5Z5 Canada for Supernus Pharmaceuticals, Inc., Rockville, MD 20850
Summary of Findings:	Oxcarbazepine extended-release is a convenient once daily formulation of oxcarbazepine, an antiepileptic drug that has demonstrated efficacy as adjunctive therapy for the treatment of partial seizures in adults and children.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☒ Fiscal Edit ☐ PDL Product
Type of PA Criteria:	☐ Increased Risk of ADE ☐ No PA Required ☐ Appropriate Indications ☒ 15 Day First Fill Fiscal Edit

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction

Partial seizures are the most common type of seizure experienced by people with epilepsy. Virtually any movement, sensory or emotional symptom can occur as part of a partial seizure, including complex visual or auditory hallucinations. In partial seizures the electrical disturbance is limited to a specific area of one cerebral hemisphere (side of the brain). Partial seizures are subdivided into simple partial seizures (in which consciousness or awareness is retained, duration 30-60 seconds) and complex partial seizures (in which consciousness is impaired or lost, duration 60-120 seconds). Partial seizures may spread or progress to a generalized tonic-clonic seizure, in which case the classification category is partial seizures secondarily generalized.

Dosage Form(s) [1]

Oxtellar XR™ is available in 150mg, 300mg and 600mg extended-release tablets containing 150mg, 300mg and 600mg respectively of oxcarbazepine.

Manufacturer

Patheon, Inc., Whitby, Ontario L1N 5Z5 Canada for Supernus Pharmaceuticals, Inc., Rockville, MD 20850

Indication(s) [1]

Adults: Adjunctive therapy in the treatment of partial seizures.
Children: Adjunctive therapy in the treatment of partial seizures in children 6 to 17 years.

Clinical Efficacy[1-12] (mechanism of action/pharmacology, comparative efficacy)

PHARMACOLOGY (1-4)

The pharmacologic activity of oxcarbazepine is primarily exerted through the 10-monohydroxy metabolite (MHD). The precise mechanism by which oxcarbazepine and MHD exert antiseizure effects is unknown; however, in vitro electrophysiologic studies indicate there is blockade of voltage-sensitive sodium channels, resulting in stabilization of hyperexcited neural membranes, inhibition of repetitive neuronal firing, and diminution of propagation of synaptic impulses. These actions are thought to be important in the prevention of seizure spread in the intact brain. In addition, increased potassium conductance and modulation of high-voltage activated calcium channels may contribute to the anticonvulsant effects. No significant interactions of oxcarbazepine or MHD with brain neurotransmitter or modulator receptor sites have been demonstrated.

PHARMACOKINETICS (1,12-14)

Oxcarbazepine is 40% protein bound with a volume of distribution of 49 L. It is extensively metabolized by the liver, to MDH, and excreted primarily in urine with a half-life of 2 hours for the parent compound and 9 hours for MDH, the active metabolite.

EFFICACY (1,4-11)
SUMMARY
Numerous well-controlled clinical trials have demonstrated the efficacy of immediate-release oxcarbazepine as adjunctive therapy for partial seizures in adults and children. In addition, a randomized, double-blind, placebo-controlled, three-arm, parallel-group clinical efficacy trial involving 366 male and female adults with refractory partial epilepsy was conducted with oxcarbazepine extended-release. Results showed that treatment with oxcarbazepine extended-release reduced seizure frequency compared with placebo. The approval was also based upon pharmacokinetic evaluations of the use of oxcarbazepine extended-release in children.

CONCLUSION (1)
Oxcarbazepine extended-release is effective as adjunctive therapy in the treatment of partial seizures in adults.

Partial seizures - Adult

STUDY DESIGN	Multicenter, randomized, double-blind, placebo-controlled, three-arm, parallel-group clinical trial (n=366).
INCLUSION CRITERIA	Male and female patients aged 18 to 65 years with refractory partial epilepsy were included. Patients had at least 3 partial seizures over 28 days during an 8-week baseline period. Subjects were receiving treatment with at least one to 3 antiepileptic drugs and were on stable treatment for a minimum of 4 weeks.
EXCLUSION CRITERIA	Subjects with a diagnosis other than partial epilepsy.
TREATMENT REGIMEN	The study included an 8-week baseline period, followed by treatment, which included a 4-week titration phase followed by a 12-week maintenance phase. The primary endpoint of the study was median percentage change from baseline in seizure frequency per 28 days during the treatment period relative to the baseline period. A total of 366 patients were enrolled at 88 sites in North America and eastern Europe. Subjects were randomized to one of 3 treatment groups and received oxcarbazepine extended-release 1200 mg/day, oxcarbazepine extended-release 2400 mg/day, or placebo.
RESULTS	The median percent change in seizure frequency compared with placebo was -9.5% for patients receiving oxcarbazepine extended-release 1200 mg/day (p=0.078) and -14.2% for patients receiving oxcarbazepine extended-release 2400 mg/day (p=0.003). Although the 1200 mg/day to placebo comparison did not reach statistical significance, concentration-response analyses revealed that the 1200 mg/day dose was an effective dose.
SAFETY	The most commonly observed adverse reactions were dizziness, somnolence, headache, balance disorder, tremor, vomiting, diplopia, asthenia, and fatigue.

Contraindications[1]

- Known hypersensitivity to oxcarbazepine or any of the product components.

Warnings and Precautions[1]

- Hyponatremia has been reported; monitor serum sodium.
- Anaphylactic reactions, angioedema have been reported; discontinue if observed; weigh risk/benefit if past history of hypersensitivity reaction.
- Serious dermatologic reactions (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis) have occurred; discontinue if observed.
- Suicidal behavior and ideation are possible; monitor for symptoms.
- Dose withdrawal should be gradual to prevent increased seizure frequency.
- Multiorgan hypersensitivity reactions have occurred; discontinue if suspected.
- Hematologic reactions (eg, pancytopenia, agranulocytosis, leukopenia) have occurred; discontinue if suspected.

Adverse Effects[1]

Most common, >= 2%	Oxtellar XR 2400 mg/day (n=123)	Oxtellar XR 1200 mg/day (n=122)	Placebo (n=121)
▪ Dizziness	41%	20%	15%
▪ Headache	15%	8%	7%
▪ Vomiting	15%	6%	9%
▪ Somnolence	14%	12%	9%
▪ Diplopia	13%	10%	4%
▪ Asthenia	7%	3%	1%
▪ Balance disorder	7%	5%	5%
▪ Fatigue	3%	6%	1%
▪ Nystagmus	3%	3%	1%
▪ Drug intolerance	2%	0%	0%
▪ Ataxia	1%	3%	1%
▪ Tremor	1%	5%	2%
▪ Vision blurred	1%	4%	3%
▪ Visual impairment	1%	3%	0%
▪ Abdominal pain, upper	0%	3%	1%
▪ Dyspepsia	0%	3%	1%
▪ Gait disturbance	0%	3%	1%
▪ Gastritis	0%	3%	2%
▪ Nasopharyngitis	0%	3%	0%
▪ Sinusitis	0%	3%	2%

Drug Interactions[1]

- Carbamazepine
- Oral contraceptives
- Phenobarbital
- Phenytoin

Dosage and Administration[1]

Adults: recommended oral dose is 1200 mg to 2400 mg once daily. Initial dose is 600 mg/day, with dose increases at weekly intervals in 600 mg/day increments. Children: dose is based on weight, with target dose of 900 mg to 1800 mg once daily. Initial dose is 8 to 10 mg/kg once daily not to exceed 600 mg/day, with titration over 2 to 3 weeks at weekly intervals in 8 to 10 mg/kg increments and not to exceed 600 mg/day. Modified initial dose: use lower doses and titrate slowly in patients with renal failure (CrCl < 30 mL/min) and geriatric patients.

Cost Comparisons (at commonly used dosages)

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST/ MONTH
*Oxcarbazepine extended-release tablets	Oxtellar XR	Supernus	150 mg tablets	1 tablet daily	$ 89.40
			300 mg tablets	1 tablet daily	$ 124.20
			600 mg tablets	1 tablet daily	$ 227.40
**Oxcarbazepine immediate-release tablets	Trileptal	Novartis	150 mg tablets	1 tablet twice daily	$ 10.80
			300 mg tablets	1 tablet twice daily	$ 14.40
			600 mg tablets	1 tablet twice daily	$ 45.00
**Oxcarbazepine immediate-release tablets	Generic	Sandoz	150 mg tablets	1 tablet twice daily	$ 10.80
			300 mg tablets	1 tablet twice daily	$ 14.40
			600 mg tablets	1 tablet twice daily	$ 45.00

*Wholesale Acquisition Cost (WAC)

**Missouri Maximum Allowable Cost (MMAC)

Conclusion

Oxcarbazepine extended-release is a once daily formulation of oxcarbazepine, an antiepileptic drug that has demonstrated efficacy as adjunctive therapy for the treatment of partial seizures in adults and children. It provides for a convenient once daily dosage form, but its comparative cost to the twice daily immediate-release oxcarbazepine will be an important factor in product selection. The application for oxcarbazepine extended-release was not referred to a US Food and Drug Administration (FDA) advisory committee because immediate-release oxcarbazepine has a well-characterized safety and efficacy profile. The manufacturer will be conducting several postmarketing pediatric studies as a requirement from the FDA.

Recommendation

The Division recommends adding this drug to the current 15 day Supply First Fill fiscal edit.

References

1. Product Information: Oxtellar XR™, oxcarbazepine extended-release tablets. Supernus Pharmaceuticals, Inc., Rockville, MD, 10/2012.
2. Grant SM & Faulds D: Oxcarbazepine: a review of its pharmacology and therapeutic potential in epilepsy, trigeminal neuralgia and affective disorders. Drugs 1992; 43:873-888.
3. Benetello P: New antiepileptic drugs. Pharmacol Res 1995; 31:155-162.
4. Bulau P & Froscher W: Oxcarbazepine as a new antiepileptic substance. Drugs Today 1991; 27:51-54.
5. Dam M: Oxcarbazepine in monotherapy. Behav Neurol 1990; 3(Suppl 1):31-34.
6. Jensen PK: Oxcarbazepine (Trileptal®) in anti-epileptic polytherapy. Behav Neurol 1990; 3(Suppl 1):35-39.
7. Dam M, Ekberg R, Loyning Y et al: A double-blind study comparing oxcarbazepine and carbamazepine in patients with newly diagnosed previously untreated epilepsy. Epilepsy Res 1989; 3:70-76.
8. Houtkooper MA, Lammertsma A, Meyer JWA et al: Oxcarbazepine (GP 47.680): a possible alternative to carbamazepine? Epilepsia 1987; 28:693-698.
9. Philbert A, Dam M & Jakobsen K: Oxcarbazepine in the treatment of epilepsy - a usable alternative to carbamazepine? Irish J Med Sci 1986; 155:297.
10. Houtkooper MA, van Oorschot C & Hoppener R: Oxcarbazepine (GP 47.680) versus carbamazepine: a double-blind crossover study in patients with epilepsy. Acta Neurol Scand 1984; 70:221-222.
11. Schachter SC, Vazquez B, Fisher RS et al: Oxcarbazepine: double-blind, randomized, placebo-control, monotherapy trial for partial seizures. Neurology 1999; 52:732-737.
12. Product Information: Tegretol®, carbamazepine. Novartis Pharmaceutical, East Hanover, NJ, 1998.

    Theisohn J & Heimann G: Disposition of the antiepileptic oxcarbazepine and its metabolites in healthy volunteers. Eur J Clin Pharmacol 1982; 22:

Prepared by: Katie Wilbers, PharmD

Date: August 26, 2013